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Culturally Adapted Cognitive-Behavioural Group Therapy for Mental Disorders in Refugees plus Problem Management Training (ReTreat): Study Protocol for a Multicentre Randomised Controlled Trial

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ABSTRACT

Introduction. Since a high proportion of refugees in Germany suffer from different mental disorders, culturally adapted treatment approaches are needed that target a broad range of symptoms and can be provided to a large number of refugees in a group setting. This RCT evaluates the efficacy of twelve-session outpatient Culturally Adapted CBT (CA-CBT+) compared to Treatment as Usual (TAU) in a sample of refugees suffering from at least one DSM-V disorder.

Methods and analysis. The present study will be carried out as two-group randomised trial with 1:1 individual allocation to either 1) CA-CBT+ in a group setting or 2) TAU. The study takes place at four sites in Germany. A total of 138 adult refugees with at least one primary DSM-5 diagnosis will be randomly assigned. In CA-CBT+ the patients receive 12 sessions of 120 min duration over the course of twelve weeks providing psychoeducation, meditation and other techniques of emotional regulation, stretching, and problem management. The primary outcome is treatment response operationalized by change in GHQ-28 score. Follow-up visits will take place 3 and 9 months after the end of the intervention. Secondary outcomes include changes in psychopathological symptoms, somatic symptoms and quality of life. Intention-to-treat (ITT) analysis will be performed. Primary and secondary outcomes will be analyzed using appropriate statistical methods.

Ethics and dissemination: The study has been approved by the Ethics Commission of the German Psychological Society (ref: StangierUlrich2019-1018VA). Results will be disseminated via presentations, publication in international journals, and national outlets for clinicians. Furthermore, intervention materials will be available, and the existing network will be used to disseminate and implement the interventions into routine health care.

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Keywords

Refugees, transcultural psychotherapy, trauma, mindfulness, yoga, stretching, culturally adapted cognitive behavioural therapy, randomised controlled trial

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Multicentre, randomised controlled trial investigating the efficacy of Culturally Adapted Cognitive Behavioural Group Therapy plus Problem Management (CA-CBT+) for asylum seekers living in Germany
- According to research CA-CBT is widely supported for adult refugees and there is currently no comparable group intervention available in mental healthcare for refugees
- Pilot trials and an ongoing RCT have shown efficacy of CA-CBT+ for treating refugees

INTRODUCTION

The majority of the refugees who came to Germany within the last years have experienced multiple traumata [1]. Furthermore, the flight itself has often been associated with traumatic, life-threatening experiences. Additional distress is caused by postmigration stressors, such as placement in provisional collective housing and insecure outcome of the asylum proceedings, contributing to the maintenance and aggravation of mental disorders [2]. Recent studies [1,3] provide evidence that refugees migrating to Western countries suffer not only from post-traumatic stress disorder (PTSD, 21-54%) but also from a variety of other mental disorders with high comorbidity rates, among them depression (20-56%), anxiety disorders (40-56%); and also somatoform symptoms (37%). Considering the large spectrum and high comorbidity of mental disorders seen in asylum seekers and refugees, a transdiagnostic approach to psychological treatment appears reasonable.

Another challenge for Western models of mental disorders and psychological treatments is to adapt interventions to the specific needs of ethnic minorities and refugee groups. Qualitative studies with Afghan [4] and Syrian refugees [5] indicate that the perception and expression of symptoms, the explanations as well as treatment expectations are linked to the specific culture. The efficacy of psychotherapy is enhanced if treatment is adapted to the culture of origin [6,7]. ReTreat will investigate the efficacy of an already existing transdiagnostic, culturally adapted approach.

In order to search for earlier clinical trials on transdiagnostic culturally adapted group treatments, we first screened meta-analyses and systematic reviews on psychological interventions in refugees and asylum seekers. In a second step, we conducted an electronic literature search using Medline, PsycINFO, Cochrane Central, the Cochrane library, clinicaltrials.gov, Deutsches Register Klinischer Studien, Google Scholar and International Clinical Trials Search Portal (date of search: October 2nd 2017). Search terms were ‘asylum seekers’, ‘refugees’, ‘group’, ‘psychotherapy’, ‘treatment’ and ‘intervention’ and their combinations for publication date 2000 to present.

According to recent meta-analyses [8,9] and systematic reviews [10], CA-CBT [6,11,12] and narrative exposure therapy are the most supported interventions for adult refugees. Whereas narrative exposure therapy has been evaluated exclusively in individual setting, however, only CA-CBT is designed for group setting. Besides, two other studies refer to group psychotherapy. One study evaluated a trauma-focused group day-treatment program for refugees, combining psychodynamic, cognitive-behavioural, psychomotor body therapy, art therapy, music therapy, and individual supportive treatment [13]. Although this day-treatment program was more effective than a waitlisted control group in reducing psychopathological symptoms, it remains unclear which components of the treatment package were effective. Furthermore, its implementation in the usual German health care system for a high number of refugees living in Germany seems difficult, because of its high-threshold and high cost day-treatment setting. Another approach to use group format in a RCT with refugees from Chechnya involved lay counselling and self-help techniques [14]. Although this approach was not less effective than traditional group CBT in reducing psychopathological symptoms, the validity of the results suffers from low statistical power. No other trials were found in the electronic databases mentioned above. The efficacy of CA-CBT was evaluated in three trials with Vietnamese refugees [11], Cambodian refugees [6], and female Latino patients with treatment-resistant PTSD [12], with effect sizes ranging from 1.6 to 2.5. However, its effects in refugee groups seen in Germany and Europe is still to be determined.

A recent pilot trial indicated that CA-CBT is an effective approach to reduce general psychopathological symptoms and to improve quality of life in Farsi speaking refugees [15]. In an ongoing RCT with a waitlist control group findings from the first trial could be replicated, indicating CA-CBT+ is an efficient program in treating refugees [16]. However, its effects in refugee groups seen in Germany and Europe is still to be determined with larger patient numbers and an active control condition.

Aims and hypotheses

The major goal of the study is to test the efficacy of transdiagnostic, culturally adapted group CBT, augmented with problem management (CA-CBT+) in a controlled, randomised multicentre trial, by comparing short- and long-term outcomes of CA-CBT+ on mental health with that of Treatment as Usual (TAU). Furthermore, we will investigate the effect of gender on the outcome of CA-CBT+. We expect that female refugees will benefit significantly more from CA-CBT+ than male refugees. Besides the effects on primary outcome, we will also test the effects of treatment on secondary outcome measures. We will test the assumption that CA-CBT+ will reduce psychopathological symptoms and somatic symptoms, and increase quality of life.

The primary hypothesis is that, (1) compared to the TAU, more participants in CA-CBT+ will benefit by reduced general psychiatric symptoms, as well as at both the 3-month and 9-month follow ups.

Additional analyses will be conducted to address the following secondary hypotheses:

(2) Participation in CA-CBT+ will reduce depressive symptoms

(3) Participation in CA-CBT+ will improve quality of life

(4) Female refugees will benefit more from CA-CBT+ than men

METHODS AND ANALYSIS

Design and setting

The present study is a multicentre, parallel two-group randomised controlled trial with 1:1 individual allocation to either: 1) culture-sensitive group program CA-CBT+ or 2) a TAU control group across four study sites in Germany (Frankfurt, Marburg, Münster, & München).

The SPIRIT statement (Standard Protocol Items: Recommendation for Interventional Trials) was used for writing this report.

Study population

The target population will comprise adult refugees from different countries of origin, mainly from Afghanistan and Syria. The full list of participant inclusion and exclusion criteria is provided in Table 1.

Table 1: Trial entry criteria

Trial entry criteria
Inclusion criteria: 1. At least one primary DSM-5 diagnosis of trauma- and stressor-related disorders, depressive disorders, anxiety disorders, or somatic symptom and related disorders confirmed by the M.I.N.I for DSM-5 2. General Health Questionnaire (GHQ-28) > 11 3. Age between 18 and 65 years 4. Informed consent In case of illiteracy, assistance will be provided in the native language or a language the patient comprehends on an advanced level of proficiency.
Exclusion criteria: 1. Current substance use disorders 2. Acute/past manic or psychotic symptoms 3. Odd/dramatic personality disorders 4. Acute suicidality 5. Severe medical conditions 6. Concurrent psychotherapy (including interventions from Sub-Projects 1 and 3).

Participant recruitment: Recruitment or patients will be conducted via established collaborations with service providers for refugees, collaborations with health care providers, a project

website, and via Social Media. The recruitment period will last for 30 months. The screening of the patients will be performed in the participating study sites. Patients will be enrolled by the local coordinator(s).

Study procedure*:* Patients will be treated at four outpatient clinics (Frankfurt, Marburg, München, and Münster). These participating sites that were selected by the Coordinating Investigators have adequate staff and experience in treating refugees with mental disorders and in conducting clinical studies. The Frankfurt and Munich sites have already established specialized refugee mental health and counselling outpatient centres. The study sites include experienced therapists regarding the targeted patient population and technical expertise to complete the protocol.

Experienced and trained therapists will administer CA-CBT+. Per site, two fully licensed psychotherapists or psychotherapists in advanced clinical training will administer CA-CBT+. All therapists will attend a 2-day workshop. The study sites include experienced therapists regarding the targeted patient population and technical expertise to complete the protocol. The duration of the study for each subject is expected to be 12 months after randomisation (see also the study flow chart in figure 1). Included are 3 months intervention period and 9 months follow-up. Screening is conducted by independent clinical raters and comprises a standardized diagnostic interview (M.I.N.I.), demographic data and an assisted self-rating of the GHQ-28. If eligible for participation in the trial, the patient is handed out the patient information and consent form. After given written consent, the patient completes secondary outcome measures at baseline (assisted self-report). In addition, medical treatment will be assessed, using the TAU protocol.

After completing baseline assessment, patients are randomised to either CA-CBT+ or TAU. Three months, six months and 12 months after randomisation, participants in the CA-CBT+ condition as well as in the TAU condition will complete secondary outcome measures (assisted self-report), and clinical raters will complete TAU protocols. At the 12 month follow-up (9 months after treatment), participants with a GHQ-28≥11 will be offered again the M.I.N.I to check the persistence of diagnoses at study

entry. In case of persisting mental problems, participants will be offered treatment at the outpatient clinics of the trial sites or transference to cooperating clinics and psychiatric services.

Randomisation

Randomisation will be performed centrally by the central office of the Coordinating Centre for Clinical Studies in Marburg. The randomisation of an eligible patient can take place if all inclusion criteria and none of the exclusion criteria are fulfilled. Therefore the Investigator completes the study specific randomisation form, which is part of the Investigator Site File (ISF), and sends it to the KKS Marburg via Mail.

The chance for allocation to the intervention group and the control group is 1:1.

The randomisation will be stratified by gender and study site to ensure balance between the two study arms across all four investigation sites. The KKS informs the centre about the randomisation result and the local coordinator(s) will assign patients to study groups. Each participant will be given a unique study code by the KKS.

Intervention

CA-CBT+ consists of 12 sessions of 120 min. duration within 12 weeks of manualized treatment. The standard session length of 120 min accommodates the need to use interpreter services in treatment. CA-CBT+ includes the following interventions: psychoeducation, meditation and other techniques of emotional regulation, stretching and problem management. All components target the transcultural and transdiagnostic hypercognitive process “thinking too much”. Based on interviews, we adapted the contents of psychoeducation such as explanations of causes, interpretations of symptoms, and therapeutic practices and concepts, to the Afghan/Iranian or Syrian/Iraqi culture. Cultural idioms of distress are used to describe mental disorders. Culture-specific causal explanations are used as a rationale for interventions (e.g. “thinking too much” for meditation). Finally, interventions are referred to culturally embedded, behavioural patterns (e.g. seeking social support).

Based on data from qualitative studies and focus groups with refugees conducted at the Frankfurt trial site of the Female Refugee Study, gender-specific topics were included in the

psychoeducation (gender-specific role behaviours, family relationships, education of children, discrimination, violence and abuse, participation in public life). The use of mental health services is often avoided due to stigma barriers, shame and taboos. We therefore present the program as a training to increase resilience, to support coping with problems and to reduce distress.

Furthermore, we added problem management training to the intervention. It has been successfully applied in the treatment of traumatized earthquake survivors in Iran [17] and in the prevention of PTSD in a conflict-affected area in Pakistan [18] We incorporated a simplified version for depression and PTSD [19] which takes into account cultural values of the participants (e.g. collective vs. individual benefit) related to the definition of goals for problem management.

Per site, two fully licensed psychotherapists or psychotherapists in advanced clinical training will administer CA-CBT+. All therapists will attend a 2-day workshop. Sessions will be audiotaped and evaluated for adherence by independent raters. Regular supervision twice a month at the four centres as well as telephone case consultation for all therapists twice a month will ensure treatment adherence.

Control Group

In the TAU condition, patients will be referred to institutions of public mental healthcare, and will be monitored at the corresponding measurement points as for CA-CBT+. Referral will be made through a standardized information leaflet. If patients are dissatisfied with their treatment after the last follow-up assessment 9 months post TAU treatment, they will be offered CA-CBT+. Patients allocated to TAU will be contacted three, six and 12 months after randomisation, and changes in medication and adverse events will be assessed using the TAU protocol.

Outcome Measures

All questionnaires will be given in the most commonly spoken native languages of the refugees. For the other questionnaires, the original versions will be translated and back-translated by different native Farsi and Arabic speakers and discrepancies clarified, in accordance with standard procedure [20]. All measures not yet translated will be translated and back-translated as is standard. When

needed, the questionnaires will be employed with support by a native-speaking or interpreter-assisted psychologist. A detailed overview of the assessments and time points is presented in

Table 2.

Diagnoses will be determined by the Mini-International Neuropsychiatric Interview 7.0 (M.I.N.I.) [21,22] adapted to DSM-5. Culturally sensitive assessment of general psychopathology will be implemented by the Afghan Symptom Checklist (ASCL) [23] or the Arab Symptom Checklist (ArSCL) [24].

An additional objective of the study is to identify predictors for short-term outcome, by using the Thinking a Lot Questionnaire (TALQ) [25] as a predictor and changes in GHQ-28 as dependent variable.

For economic analysis of CA-CBT+, costs will be measured by a brief version of the Client Sociodemographic and Service Receipt Inventory (CSSRI) [26], utilities will be assessed by the EuroQol (EQ-5D) [27]. Healthcare utilisation will be monetarily valued by unit costs. By synthesizing costs and (clinical) outcomes, the cost analyses will be extended to a cost-effectiveness analysis or/and a cost-utility analysis depending on data quality. Economic outcomes include the incremental cost-effectiveness ratio (ICER) and cost-effectiveness acceptability curves (CEACs) based on net-benefit regression to adjust for potential confounding. Therapy expectations will be assessed via four items.

Primary endpoint

The GHQ–28 [28] is a widely used instrument for the assessment of psychiatric symptoms in general population surveys, primary care, and general medical outpatients. It consists of 28 items grouped into four subscales: Somatic symptoms, Anxiety and insomnia, Social dysfunction, and severe depression. The items are rated on a four-point Likert scale, which is recommended to be transformed into a binary scale (0,1=0; 2,3=1). The GHQ-28 has also been validated for Arabic [29] and Afghan populations [30], and as CSA measure of change in psychiatric patients, using the Present State Examination as criterion. Therefore, we based the definition of treatment response on the GHQ-28. Definition of response to treatment was derived from the findings of Ormel et al. [31]. In their study, patients from a psychiatric sample underwent psychiatric treatment and were classified as recovered, unchanged or deteriorated. Based on these findings, we defined clinical significant improvement either

as a decrease in the GHQ-28 score of -5 or more or change to recovery by decreasing below the threshold for psychiatric conditions of less than 5.

Secondary endpoints

Sociodemographic data such as information on gender, age, education, country of origin, duration of stay in Germany, command of language, family status, residence status and current living conditions are collected during screening from all participants.

Depressive symptoms will be assessed using the Patient Health Questionnaire (PHQ-9) [32]. The International Trauma Questionnaire (ITQ) [33] is a brief self-report measure and contains 12 items. It measures the core features of PTSD and CPTSD and is consistent with the criteria from ICD-11. The Somatic Symptom Scale (SSS-8) will be used to measure somatic symptoms [34,35]. Health-related quality of life will be assessed using the international standard Euroqol-5D (EQ-5D) [27]. Good psychometric properties of the EQ-5D have been reported in different languages, including Arabic. The Post-Migration Living Difficulties Checklist (PMLDC) [36] is a self-report questionnaire used to assess recent adverse life experiences typical of migration. The Client Satisfaction Questionnaire (CSQ-8) [37], an 8-item self-report instrument constructed to measure satisfaction with health services, will be used at post-assessment. To assess long-term effects of treatment, the measurements will be taken at three and nine months after treatment. A 3-month follow-up reflects the standard in studies with refugees. However, a nine months interval after randomisation allows for the assessment of long-term maintenance of treatment effects.

Table 2: Summary of assessment schedule

Visit	Screen.	Base-line		**Intervention Visits 1 - 12**											**End of inter-vention**	**FU1**	**FU2**
Week	0	0		1	2	3	4	5	6	7	8	9	10	11	12	24	52
Day	0	1		7	14	21	28	35	42	49	56	63	70	77	84	168	364
MINI	D																
Demographic data	D																
GHQ-28	P														P	P	P
PHQ-9		P													P	P	P
ITQ		P													P	P	P
SSS-8		P													P	P	P
Therapy Expectations		P															
EQ-5D		P													P	P	P
CSSRI		P														P	P
CSSRI brief															P		
PMLDC		P													P	P	P
ASCL/ArSCL		P													P	P	P
CSQ-8		P													P		P
TALQ				T													
Diagnosis, meeting inclusion criteria	D																
Informed consent	P																
Adherence and Competence Rating				T	T	T	T	T	T	T	T	T	T	T			
TAU protocols	D		**Random assignment by KKS**												D	D	D

Notes: T: rated by therapists (CA-CBT+); P: rated by patients (assisted) D: rated by independent clinical raters

Blinding

To avoid detection bias, study personnel conducting the assessments will be blinded. Blinding of therapists and patients is not possible. To avoid detection bias, treatment effects will be assessed by using self-report measures. However, participants will be assisted by psychologists who are blinded to group allocation. Additionally, to prevent selection bias, randomisation will be performed externally by the KKS.

Sample size

Our sample size calculation is based on the assumption that the primary endpoint will take on higher values in women than in men. In accordance with demographic data in Germany the gender ratio in the participants is estimated as 67% men vs. 33% women. Estimates for % patients with response are as follows: a) women: CA-CBT =66.0%, TAU=32.65%; b) men: CA-CBT =58.1%, TAU=25.7%. In order to detect an odds ratio of 4 in each stratum between groups at a two-sided α of 5% with a power of 80%, 82 persons (41 per group) are required (Cochran Mantel-Haenszel test, software PASS 14, version 14.0.4, NCSS, LLC). Compensating for 40% dropouts, 138 patients have to be randomised.

Adverse Events

Complications are divided into Serious Adverse Events (SAEs) and Adverse Events (AEs). The following events are categorized as SAEs: (1) Suicide; (2) Other cause of death; (3) Severe self-harm; (4) Harm of others; (5) Suicide attempt; (6) Life-threatening event (participant is in acute risk of death) and (7) Event that led to severe physical disability. The following events are categorized as AEs: (1) Occurrence of new symptoms of a severe mental disorder; (2) Unforeseen or prolonged hospitalization due to psychiatric problems and (3) Clinically significant worsening of clinical symptoms such as exacerbation of PTSD symptoms, suicidal ideation, psychotic symptoms indications of substance misuse or body symptoms that have to be medically evaluated (e.g. cardiac arrhythmia).

(S)AEs are documented if reported. All SAEs and AEs will be recorded in the participant file and the eCRF for the duration of the participant's direct involvement in the trial. All SAEs and AEs must be

reported to the Coordinating Investigators, and the central project manager within 24 hours upon notice of the event.

End of protocol treatment

Study treatment of a patient may also be terminated by the investigator for one of the following reasons: (a) Severe Serious Complications which makes it necessary to stop the study treatment, (b) Abnormal test procedure result(s) which make it necessary to stop study treatment, or (c) Non-compliance with the study protocol. Study treatment must be terminated for one of the following reasons: (a) Withdrawal of patient's consent to study treatment or (b) Study treatment termination by the investigator. If the investigator terminates the treatment of the patient prematurely, he has to inform the patient about his decision and has to record the primary reason for withdrawal in the patient file and to document the end of treatment in the CRF. If the patient caused the premature withdrawal the data collected before termination may be used if the patient agrees and an informed consent for follow up is signed by the patient.

Data management

The trial will use an electronic case report form (e-CRF/EDC-System) for data collection and documentation, which is hosted by KKS Marburg. The data will be entered directly via web browser to the e-CRF and are transferred via encryption (HTTPS (TSL/SSL)) to the central database. Access to the e-CRF is only allowed for persons who are documented as trial personnel and have received necessary training. Each person who is allowed to make entries in the e-CRF receives a personal username and the URL for database login upon request (User-ID request).

The given data will be checked electronically for its plausibility and consistency in a multistage procedure. Detected inconsistencies and missing or implausible data will be clarified with queries (electronically or paper-based) and necessary changes will be carried out. The EDC system has an implemented audit trail. This assures that any documentation and/or changes to database items are traceable anytime. At the end of trial, the database will be closed after data cleaning process. This

process will be documented according to SOPs of KKS Marburg. The pseudonymized patient data recorded in the e-CRF are stored by the KKS Marburg in accordance with legal requirements.

Statistical analysis

Primary outcome:

The null hypothesis "no difference in the primary endpoint between the CA-CBT+ and TAU group" will be tested against the alternative hypothesis "difference in the primary endpoint between the CA-CBT+ and TAU group" by a two-sided Cochran Mantel-Haenszel test stratified for gender at α = 5 %. Estimates for the primary endpoint in each group and corresponding 95% confidence intervals will be presented. In addition, multivariable binary logistic regression analyses will be performed to analyze the influence of baseline covariates. The analysis will also be performed for the per-protocol population as sensitivity analysis.

Secondary outcome:

Both absolute changes in continuous scores as well as categorical assessments of GHQ-28 total score and subscales for Depression, Somatic Symptoms, Anxiety, and the International Trauma Questionnaire (ITQ) from T1 to T2, Client Satisfaction Scale at T2 will be analysed by appropriate hierarchical regression models (i.e. Poisson or Binomial model) adjusting for baseline covariates. Furthermore, longitudinal analyses will be performed by applying (generalized) linear mixed models with first order autoregressive covariance matrices (repeated measures analyses) and random effects for patient and center, main effects for group, gender and time, as well as interaction terms for group-by-time and group-by-gender. All efficacy analyses will be performed for the intention-to-treat population.

Safety and tolerability endpoints

Multiple imputation of missing values will be applied according to Rubin's concept (data missing completely at random, missing at random, and missing not at random). Sensitivity analyses will be performed to investigate the effect of different modelling strategies for the imputation of missing values on the primary endpoint.

Monitoring

An independent Data Safety and Monitoring Board (DSMB) has been established. The DSMB will periodically review the accumulating data and patient safety. Based upon their review, the DSMB will determine if the trial should be modified and make recommendations to the Coordinating Investigators. The DSMB independent from the study organizers and sponsors.

Patient and public involvement

The development of CA CBT+ was supported by key informants, native speakers, and interpreters as well as experienced counsellors that work in this field as described in prior pilot and randomised controlled trials **[15,16]**.

Authors' contributions: US, SK, and AN wrote the first draft of the manuscript; US is the principal investigator, and SK is the study coordinator for ReTreat; JPR, CSB, AK, JG, TE, CW, and RNM contributed to the conceptualisation of the study design. RM, NM, TE are study site leaders. All authors critically evaluated and commented on the manuscript and have given final approval of the manuscript.

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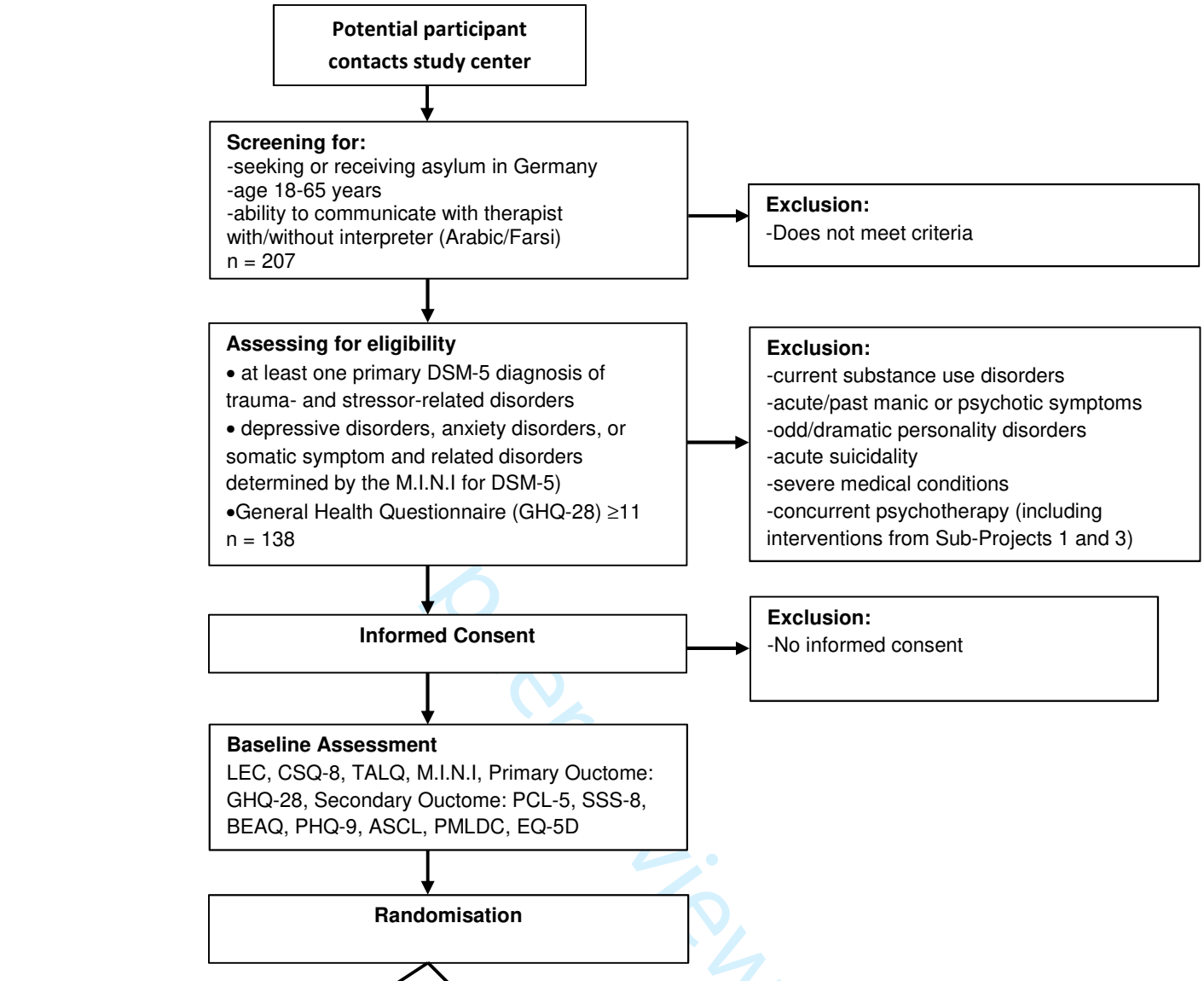
Figure Legend:

Figure 1 - Study flowchart of the ReTreat randomised controlled trial, TAU, treatment as usual.



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Culturally Adapted Cognitive-Behavioural Group Therapy for Mental Disorders in Refugees plus Problem Solving Training (ReTreat): Study Protocol for a Multicentre Randomised Controlled Trial

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Culturally Adapted Cognitive-Behavioural Group Therapy for Mental Disorders in Refugees plus Problem Solving Training (ReTreat): Study Protocol for a Multicentre Randomised Controlled Trial

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ABSTRACT

Introduction. Since a high proportion of refugees in Germany suffer from mental disorders, culturally adapted treatments are needed that target a broad range of symptoms . There is much evidence for the efficacy of CA-CBT. Given the promising results of CA-CBT, the combination with problem solving training (CA-CBT+) represents a novel approach that potentially improves the refugees' ability to cope actively with psychosocial problems. This RCT evaluates the efficacy of twelve-session outpatient CA-CBT+ compared to Treatment as Usual (TAU) in a sample of refugees suffering from at least one DSM-V disorder.

Methods and analysis. The present study will be carried out as two-group randomised trial with 1:1 individual allocation to either 1) Culturally-adapted Cognitive Behavioral Therapy in a group setting (CA-CBT+) or 2) treatment as usual (TAU). The study takes place at four sites in Germany, randomising in total 138 adult refugees with at least one primary DSM-5 diagnosis to the treatment conditions. In CA-CBT+ the patients receive 12 sessions of 120 min duration over the course of twelve weeks providing psychoeducation, meditation and other techniques of emotional regulation, stretching, and problem solving training. The primary outcome is treatment response operationalized by a clinically significant change in GHQ-28 score. Follow-up visits will take place 3 and 9 months after the end of the intervention. Secondary outcomes include changes in psychopathological symptoms, somatic symptoms and quality of life. Intention-to-treat (ITT) analysis will be performed. Adverse and serious adverse events will be analyzed. Further, healthcare utilization and economic outcomes will be assessed and analyzed. Primary and secondary outcomes will be analyzed using appropriate statistical methods.

Ethics and dissemination: The study has been approved by the Ethics Commission of the German Psychological Society (ref: StangierUlrich2019-1018VA). Results will be disseminated via presentations, publication in international journals, and national outlets for clinicians. Furthermore, intervention materials will be available, and the existing network will be used to disseminate and implement the interventions into routine health care.

Trial Registration Number: DRKS00021536, Date of registration: 2020-07-08).

Protocol Version: 2020-20-11, Version Number: VO1

Keywords

Refugees, transcultural psychotherapy, trauma, mindfulness, yoga, stretching, culturally adapted cognitive behavioural therapy, randomised controlled trial

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength of our study is the multicenter randomised controlled design with a relatively large sample size
- Another advantage is that the cultural adaptation was implemented according to a standardized framework and previously published
- Another strength is the evaluation of healthcare utilization and the economic analysis
- A major limitation is the lack of an alternative intervention in the control condition
- Another limitation is that the study design does not allow any conclusions about the incremental efficacy of the cultural adaptation compared to regular CBT

INTRODUCTION

The majority of the refugees from the Middle East in Germany have experienced multiple traumata [1]. Furthermore, the flight itself has often been associated with traumatic, life-threatening experiences. Additional distress is caused by postmigration stressors, such as placement in provisional collective housing and insecure outcome of the asylum proceedings, contributing to the maintenance and aggravation of mental disorders [2]. Recent studies [1,3] provide evidence that refugees migrating to Western countries suffer not only from post-traumatic stress disorder (PTSD, 21-54%) but also from a variety of other mental disorders with high comorbidity rates, among them depression (20-56%), anxiety disorders (40-56%); and also somatoform symptoms (37%). Considering the large spectrum and high comorbidity of mental disorders seen in asylum seekers and refugees, a transdiagnostic approach to psychological treatment appears reasonable.

Another challenge for Western models of mental disorders and psychological treatments is to adapt interventions to the specific needs of ethnic minorities and refugee groups. Qualitative studies with Afghan [4] and Syrian refugees [5] indicate that the perception and expression of symptoms, the explanations as well as treatment expectations are linked to the specific culture. The efficacy of psychotherapy is enhanced if treatment is adapted to the culture of origin [6,7, 8]. In addition, several researchers have developed frameworks to standardize the process of cultural adaptation [9, 10].

In accordance with these guidelines, the first step of cultural adaptation of the present treatment was screen clinical trials, meta-analyses and systematic reviews on culturally adapted psychological interventions in refugees and asylum seekers. We conducted an electronic literature search using Medline, PsycINFO, Cochrane Central, the Cochrane library, clinicaltrials.gov, Deutsches Register Klinischer Studien, Google Scholar and International Clinical Trials Search Portal (date of search: October 2nd 2017). Search terms were ‘asylum seekers’, ‘refugees’, ‘group’, ‘psychotherapy’, ‘treatment’ and ‘intervention’ and their combinations for publication date 2000 to present.

According to recent meta-analyses [11,12] and systematic reviews [13], CA-CBT [6,14,15] and narrative exposure therapy are the most supported interventions for adult refugees. Whereas narrative exposure therapy has been evaluated exclusively in individual setting, however, only CA-CBT is designed for group setting. Besides, two other studies refer to group psychotherapy. One study evaluated a trauma-focused group day-treatment program for refugees, combining psychodynamic, cognitive-behavioural and a number of other treatment approaches [16]. Although this day-treatment program was more effective than a waitlisted control group in reducing psychopathological symptoms, its implementation is impeded by the requirements for different treatment components and the high costs for day-treatment setting. Another approach to use group format in a RCT with refugees from Chechnya involved lay counselling and self-help techniques [17]. Although this approach was not less effective than traditional group CBT in reducing psychopathological symptoms, the validity of the results suffers from low statistical power. No other trials with group treatments were identified in the electronic databases. CA-CBT was evaluated in three trials with Vietnamese refugees [14], Cambodian refugees [6], and female Latino patients with treatment-resistant PTSD [15], yielding large effect sizes ranging from 1.6 to 2.5. However, its efficacy in refugee samples in Germany and Europe is still to be determined.

A recent pilot trial indicated that CA-CBT is an effective approach to reduce general psychopathological symptoms and to improve quality of life in Farsi speaking refugees [18]. In addition, the adaptation process was implemented according to a standardized framework for cultural adaptation and previously published [19]. In an ongoing RCT with a waitlist control group the positive findings from the first trial were replicated, indicating CA-CBT+ is an efficient program in treating refugees [20]. However, the RCT trial had a waiting list control condition and a relatively small sample size of 24 participants. Thus, the efficacy of CA CBT+ in refugee groups seen in Germany and Europe is still to be determined with larger patient numbers and an active control condition. In order to evaluate the potential implications for the healthcare system, the assessment of healthcare utilisation and economic analysis are needed.

Aims and hypotheses

The major goal of the study is to test the efficacy of transdiagnostic, culturally adapted group CBT, augmented with problem solving training (CA-CBT+) in a controlled, randomised multicentre trial, by comparing short- and long-term outcomes of CA-CBT+ on mental health with Treatment as Usual (TAU). Furthermore, we will investigate the effect of gender on the outcome of CA-CBT+. Recent findings indicate that male gender is associated with a higher number of non-responders in refugees [21]. Therefore, we expect that female refugees will benefit significantly more from CA-CBT+ than male refugees. Besides the effects on primary outcome, we will also test the effects of treatment on secondary outcome measures, including psychopathological symptoms and somatic symptoms and quality of life.

The primary hypothesis is that, (1) compared to the TAU, more participants in CA-CBT+ will show reduced general psychiatric symptoms, as well as at both the 3-month and 9-month follow ups.

Additional analyses will be conducted to address the following secondary hypotheses:

(2) Participation in CA-CBT+ will reduce depressive symptoms

(3) Participation in CA-CBT+ will improve quality of life

(4) Female refugees will benefit more from CA-CBT+ than men

METHODS AND ANALYSIS

Design and setting

The present study is a multicentre, parallel two-group randomised controlled trial with 1:1 individual allocation to either: 1) culture-sensitive group program CA-CBT+ or 2) a TAU control group across four study sites in Germany (Frankfurt, Marburg, Münster, & München). The study is planned start on 01/09/20 and to be concluded on 01/01/2024.

The SPIRIT statement (Standard Protocol Items: Recommendation for Interventional Trials) was used for writing this report.

Study population

The target population will comprise adult refugees from different countries of origin, mainly from Afghanistan and Syria. The full list of participant inclusion and exclusion criteria is provided in Table 1.

Table 1: Trial entry criteria

Trial entry criteria
Inclusion criteria: 1. At least one primary DSM-5 diagnosis of trauma- and stressor-related disorders, depressive disorders, anxiety disorders, or somatic symptom and related disorders confirmed by the M.I.N.I for DSM-5 2. General Health Questionnaire (GHQ-28) > 11 3. Age between 18 and 65 years 4. Informed consent In case of illiteracy, assistance will be provided in the native language or a language the patient comprehends on an advanced level of proficiency.
Exclusion criteria: 1. Current substance use disorders 2. Acute/past manic or psychotic symptoms 3. Odd/dramatic personality disorders 4. Acute suicidality 5. Severe medical conditions 6. Concurrent psychotherapy (including interventions from Sub-Projects 1 and 3).

Participant recruitment: Recruitment or patients will be conducted via established collaborations with service providers for refugees, collaborations with health care providers, a project

website, and via social media. The recruitment period will last for 30 months. The screening of the patients will be performed in the participating study sites. Patients will be enrolled by the local coordinator(s).

Study procedure*:* Patients will be treated at four outpatient clinics (Frankfurt, Marburg, München, and Münster). These participating sites that were selected by the Coordinating Investigators have adequate staff and experience in treating refugees with mental disorders and in conducting clinical studies. The Frankfurt and Munich sites have already established specialized refugee mental health and counselling outpatient centres. The study sites include experienced therapists regarding the targeted patient population and technical expertise to complete the protocol.

Experienced and trained therapists will administer CA-CBT+. Per site, two fully licensed psychotherapists or psychotherapists in advanced clinical training will administer CA-CBT+. All therapists will attend a 2-day training in CA CBT +. The study sites include experienced therapists regarding the targeted patient population and technical expertise to complete the protocol. The duration of the study for each subject is expected to be 12 months after randomisation (see also the study flow chart in figure 1). Included are 3 months intervention period and 9 months follow-up. Screening will be conducted by independent clinical raters and comprises a standardized diagnostic interview (M.I.N.I.), demographic data and an assisted self-rating of the GHQ-28. If eligible for participation in the trial, the patient is handed out the patient information and consent form. After given written consent, the patient completes secondary outcome measures at baseline (assisted self-report). In addition, medical treatment will be assessed, using the TAU protocol. Due to the high number of measures interviewers will be trained in advance and a guideline will be provided, to reduce potential stress for participants.

After completing baseline assessment, patients will be randomised to either CA-CBT+ or TAU. Three months, six months and 12 months after randomisation, participants in the CA-CBT+ condition as well as in the TAU condition will complete secondary outcome measures (assisted self-report), and clinical raters will complete TAU protocols. At the 12 month follow-up (9 months after treatment),

participants with a GHQ-28≥11 will be offered again the M.I.N.I to check the persistence of diagnoses at study entry. In case of persisting mental problems, participants will be offered treatment at the outpatient clinics of the trial sites or cooperating clinics and psychiatric services.

Patient and public involvement

No patient involved.

Randomisation

Randomisation will be performed centrally by the central office of the Coordinating Centre for Clinical Studies in Marburg. The randomisation of an eligible patient can take place if all inclusion criteria and none of the exclusion criteria are fulfilled.

The chance for allocation to the intervention group and the control group is 1:1.

The randomisation will be stratified by gender and study site to ensure balance between the two study arms across all four investigation sites. The Coordination Center for Clinical trials (KKS) in Marburg informs the centre about the randomisation result and the local coordinator(s) will assign patients to study groups. Each participant will be given a unique study code by the KKS.

Intervention

CA-CBT+ consists of 12 weekly sessions of 120 min. duration [22]. The standard session length of 120 min accommodates the need to use interpreter services in treatment. CA-CBT+ includes the following interventions: psychoeducation, meditation and other techniques of emotional regulation, cognitive techniques (e.g. identification of the relationship between thoughts, emotions, and somatic complaints), and stretching. All components target “thinking too much” as a transcultural concept of mental suffering. Furthermore, we added problem solving training to the intervention. A focus group that was conducted after the pilot trial, revealed the lack of interventions that address post migration stressors. The implementation of problem solving techniques intended to enable patients to take independent actions within their social contexts. As a less intense intervention delivered by non-professional helpers, problem management + has been successfully applied in the treatment of traumatized earthquake survivors in Iran [23] and in the prevention of PTSD in a conflict-affected area

in Pakistan [24]. We incorporated simplified, easier accessible rationales for depression and PTSD symptoms [25] which take into account cultural values of the participants (e.g. collective vs. individual benefit) or the varying mental health literacy.

Based on interviews, we adapted the contents of psychoeducation such as explanations of causes, interpretations of symptoms, and therapeutic practices and concepts, to the Afghan/Iranian or Syrian/Iraqi culture (for further details please see 19). Cultural idioms of distress are used to describe mental disorders. Culture-specific causal explanations are used as a rationale for interventions (e.g. "thinking too much" for meditation). Finally, interventions are referred to culturally embedded, behavioural patterns (e.g. seeking social support).

Based on data from qualitative studies and focus groups with refugees conducted at the Frankfurt trial site of the Female Refugee Study, gender-specific topics were included in the psychoeducation (gender-specific role behaviours, family relationships, education of children, discrimination, violence and abuse, participation in public life). The use of mental health services is often avoided due to stigma barriers, shame and taboos. We therefore present the program as a training to increase resilience, to support coping with problems and to reduce distress.

Per site, two fully licensed psychotherapists or psychotherapists in advanced clinical training will administer CA-CBT+. All therapists will attend an additional 2-day CA-CBT+ workshop. Sessions will be audiotaped and evaluated for adherence by independent raters. Regular supervision twice a month at the four centres as well as telephone case consultation for all therapists twice a month will ensure treatment adherence.

Control Group

In the TAU condition, patients will be referred to institutions of public mental healthcare, and will be monitored at the corresponding measurement points as for CA-CBT+. Referral will be made through a standardized information leaflet. TAU may include drug treatment, and supportive counselling. If patients are dissatisfied with their treatment after the last follow-up assessment 9 months post TAU treatment, they will be offered CA-CBT+. Patients allocated to TAU will be contacted

three, six and 12 months after randomisation, and changes in medication and adverse events will be assessed using the TAU protocol.

Outcome Measures

All questionnaires will be given in the most commonly spoken native languages of the refugees. For the other questionnaires, the original versions will be translated and back-translated by different native Farsi and Arabic speakers and discrepancies clarified, in accordance with standard procedure [26]. All measures not yet translated will be translated and back-translated as is standard. When needed, the questionnaires will be employed with support by a native-speaking or interpreter-assisted psychologist. A detailed overview of the assessments and time points is presented in

Table 2.

Diagnoses will be determined by the Mini-International Neuropsychiatric Interview 7.0 (M.I.N.I.) [27,28] adapted to DSM-5. Culturally sensitive assessment of general psychopathology will be implemented by the Afghan Symptom Checklist (ASCL) [29] or the Arab Symptom Checklist (ArSCL) [30].

An additional objective of the study is to identify predictors for short-term outcome, by using the Thinking a Lot Questionnaire (TALQ) [31] as a predictor and changes in GHQ-28 as dependent variable.

For economic analysis of CA-CBT+, costs will be measured by a brief version of the Client Sociodemographic and Service Receipt Inventory (CSSRI) [32], utilities will be assessed by the EuroQol (EQ-5D) [33]. Healthcare utilisation will be monetarily valued by unit costs. By synthesizing costs and (clinical) outcomes, the cost analyses will be extended to a cost-effectiveness analysis or/and a cost-utility analysis depending on data quality. Economic outcomes include the incremental cost-effectiveness ratio (ICER) and cost-effectiveness acceptability curves (CEACs) based on net-benefit regression to adjust for potential confounding. Therapy expectations will be assessed via four items.

Primary endpoint

The GHQ–28 [34] is a widely used instrument for the assessment of psychiatric symptoms in general population surveys, primary care, and general medical outpatients. It consists of 28 items grouped into four subscales: Somatic symptoms, Anxiety and insomnia, Social dysfunction, and severe depression. The items are rated on a four-point Likert scale, which is recommended to be transformed into a binary scale (0,1=0; 2,3=1). The GHQ-28 has also been validated for Arabic [35] and Afghan populations [36], and as CSA measure of change in psychiatric patients, using the Present State Examination as criterion. Therefore, we based the definition of treatment response on the GHQ-28. Definition of response to treatment was derived from the findings of Ormel et al. [37]. In their study, patients from a psychiatric sample underwent psychiatric treatment and were classified as recovered, unchanged or deteriorated. Based on these findings, we defined clinical significant improvement either

as a decrease in the GHQ-28 score of -5 or more or change to recovery by decreasing below the threshold for psychiatric conditions of less than 5.

Secondary endpoints

Sociodemographic data such as information on gender, age, education, country of origin, duration of stay in Germany, command of language, family status, residence status and current living conditions are collected during screening from all participants.

Depressive symptoms will be assessed using the Patient Health Questionnaire (PHQ-9) [38]. The International Trauma Questionnaire (ITQ) [39] is a brief self-report measure and contains 12 items. It measures the core features of PTSD and CPTSD and is consistent with the criteria from ICD-11. The Somatic Symptom Scale (SSS-8) will be used to measure somatic symptoms [40,41]. Health-related quality of life will be assessed using the international standard Euroqol-5D (EQ-5D) [33]. Good psychometric properties of the EQ-5D have been reported in different languages, including Arabic. The Post-Migration Living Difficulties Checklist (PMLDC) [42] is a self-report questionnaire used to assess recent adverse life experiences typical of migration. The Client Satisfaction Questionnaire (CSQ-8) [43], an 8-item self-report instrument constructed to measure satisfaction with health services, will be used at post-assessment. To assess long-term effects of treatment, the measurements will be taken at three and nine months after treatment. A 3-month follow-up reflects the standard in studies with refugees. However, a nine months interval after randomisation allows for the assessment of long-term maintenance of treatment effects.

Table 2: Summary of assessment schedule

Visit	Screen.	Base-line		**Intervention Visits 1 - 12**											**End of inter-vention**	**FU1**	**FU2**
Week	0	0		1	2	3	4	5	6	7	8	9	10	11	12	24	52
Day	0	1		7	14	21	28	35	42	49	56	63	70	77	84	168	364
MINI	D																
Demographic data	D																
GHQ-28	P														P	P	P
PHQ-9		P													P	P	P
ITQ		P													P	P	P
SSS-8		P													P	P	P
Therapy Expectations		P															
EQ-5D		P													P	P	P
CSSRI		P														P	P
CSSRI brief															P		
PMLDC		P													P	P	P
ASCL/ArSCL		P													P	P	P
CSQ-8		P													P		P
TALQ				T													
Diagnosis, meeting inclusion criteria	D																
Informed consent	P																
Adherence and Competence Rating				T	T	T	T	T	T	T	T	T	T	T			
TAU protocols	D		**Random assignment by KKS**												D	D	D

Notes: T: rated by therapists (CA-CBT+); P: rated by patients (assisted) D: rated by independent clinical raters

Blinding

To avoid detection bias, study personnel conducting the assessments will be blinded. Blinding of therapists and patients is not possible. To avoid detection bias, treatment effects will be assessed by using self-report measures. However, participants will be assisted by psychologists who are blinded to group allocation. Additionally, to prevent selection bias, randomisation will be performed externally by the KKS.

Sample size

Our sample size calculation is based on the assumption that the primary endpoint will take on higher values in women than in men. In accordance with demographic data in Germany the gender ratio in the participants is estimated as 67% men vs. 33% women. Estimates for % patients with response are as follows: a) women: CA-CBT =66.0%, TAU=32.65%; b) men: CA-CBT =58.1%, TAU=25.7%. In order to detect an odds ratio of 4 in each stratum between groups at a two-sided α of 5% with a power of 80%, 82 persons (41 per group) are required (Cochran Mantel-Haenszel test, software PASS 14, version 14.0.4, NCSS, LLC). Compensating for 40% dropouts, 138 patients have to be randomised. Participants who did not attend to 50% of appointments or at least four consecutive appointments will be classified as dropouts.

Adverse Events

Complications are divided into Serious Adverse Events (SAEs) and Adverse Events (AEs). The following events are categorized as SAEs: (1) Suicide; (2) Other cause of death; (3) Severe self-harm; (4) Harm of others; (5) Suicide attempt; (6) Life-threatening event (participant is in acute risk of death) and (7) Event that led to severe physical disability. The following events are categorized as AEs: (1) Occurrence of new symptoms of a severe mental disorder; (2) Unforeseen or prolonged hospitalization due to psychiatric problems and (3) Clinically significant worsening of clinical symptoms such as exacerbation of PTSD symptoms, suicidal ideation, psychotic symptoms indications of substance misuse or body symptoms that have to be medically evaluated (e.g. cardiac arrhythmia).

(S)AEs are documented if reported. All SAEs and AEs will be recorded in the participant file and the eCRF for the duration of the participant's direct involvement in the trial. All SAEs and AEs must be reported to the Coordinating Investigators, and the central project manager within 24 hours upon notice of the event.

End of protocol treatment

Study treatment of a patient may also be terminated by the investigator for one of the following reasons: (a) Severe Serious Complications which makes it necessary to stop the study treatment, (b) Abnormal test procedure result(s) which make it necessary to stop study treatment, or (c) Non-compliance with the study protocol. Study treatment must be terminated for one of the following reasons: (a) Withdrawal of patient's consent to study treatment or (b) Study treatment termination by the investigator. If the investigator terminates the treatment of the patient prematurely, he has to inform the patient about his decision and has to record the primary reason for withdrawal in the patient file and to document the end of treatment in the CRF. If the patient caused the premature withdrawal the data collected before termination may be used if the patient agrees and an informed consent for follow up is signed by the patient.

Data management

The trial will use an electronic case report form (e-CRF/EDC-System) for data collection and documentation, which is hosted by KKS Marburg. The data will be entered directly via web browser to the e-CRF and are transferred via encryption (HTTPS (TSL/SSL)) to the central database. Access to the e-CRF is only allowed for persons who are documented as trial personnel and have received necessary training. Each person who is allowed to make entries in the e-CRF receives a personal username and the URL for database login upon request (User-ID request).

The given data will be checked electronically for its plausibility and consistency in a multistage procedure. Detected inconsistencies and missing or implausible data will be clarified with queries (electronically or paper-based) and necessary changes will be carried out. The EDC system has an

implemented audit trail. This assures that any documentation and/or changes to database items are traceable anytime. At the end of trial, the database will be closed after data cleaning process. This process will be documented according to SOPs of KKS Marburg. The pseudonymized patient data recorded in the e-CRF are stored by the KKS Marburg in accordance with legal requirements.

Statistical analysis

Primary outcome:

The null hypothesis "no difference in the primary endpoint between the CA-CBT+ and TAU group" will be tested against the alternative hypothesis "difference in the primary endpoint between the CA-CBT+ and TAU group" by a two-sided Cochran Mantel-Haenszel test stratified for gender at α = 5 %. Estimates for the primary endpoint in each group and corresponding 95% confidence intervals will be presented. In addition, multivariable binary logistic regression analyses will be performed to analyze the influence of baseline covariates and the language of adaptation (Farsi vs. Arabic). In addition, a mixed ANOVA will be conducted to test for language-specific group effects on the GHQ-28. The analysis will also be performed for the per-protocol population as sensitivity analysis.

Secondary outcome:

Both absolute changes in continuous scores as well as categorical assessments of GHQ-28 total score and subscales for Depression, Somatic Symptoms, Anxiety, and the International Trauma Questionnaire (ITQ) from T1 to T2, Client Satisfaction Scale at T2 will be analysed by appropriate hierarchical regression models (i.e. Poisson or Binomial model) adjusting for baseline covariates. Furthermore, longitudinal analyses will be performed by applying (generalized) linear mixed models with first order autoregressive covariance matrices (repeated measures analyses) and random effects for patient and center, main effects for group, gender and time, as well as interaction terms for group-by-time and group-by-gender. All efficacy analyses will be performed for the intention-to-treat population.

Safety and tolerability endpoints

Multiple imputation of missing values will be applied according to Rubin's concept (data missing completely at random, missing at random, and missing not at random). Sensitivity analyses will be performed to investigate the effect of different modelling strategies for the imputation of missing values on the primary endpoint.

Monitoring

An independent Data Safety and Monitoring Board (DSMB) has been established. The DSMB will periodically review the accumulating data and patient safety. Based upon their review, the DSMB will determine if the trial should be modified and make recommendations to the Coordinating Investigators. The DSMB independent from the study organizers and sponsors.

Ethics and dissemination

The study has been approved by the Ethics Commission of the German Psychological Society (ref: StangierUlrich2019-1018VA). Results will be disseminated via presentations, publication in international journals, and national outlets for clinicians. Furthermore, intervention materials will be available, and the existing network will be used to disseminate and implement the interventions into routine health care.

The trial will be conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and will follow the principles of Good Clinical Practice. Members of the IDSMB, the principal investigators, as well as the KKS Marburg will ensure adherence to these guidelines.

After trial completion and publication of the study results, data requests can be submitted to the principal investigators.

Authors' contributions: US, SK, and AN wrote the first draft of the manuscript; US is the principal investigator, and SK is the study coordinator for ReTreat; JPR, CSB, AK, HS, JG, TE, CW, and RNM contributed to the conceptualisation of the study design. RM, NM, TE are study site leaders. All authors critically evaluated and commented on the manuscript and have given final approval of the manuscript.

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Competing interests statement: The authors have no competing interest to declare.

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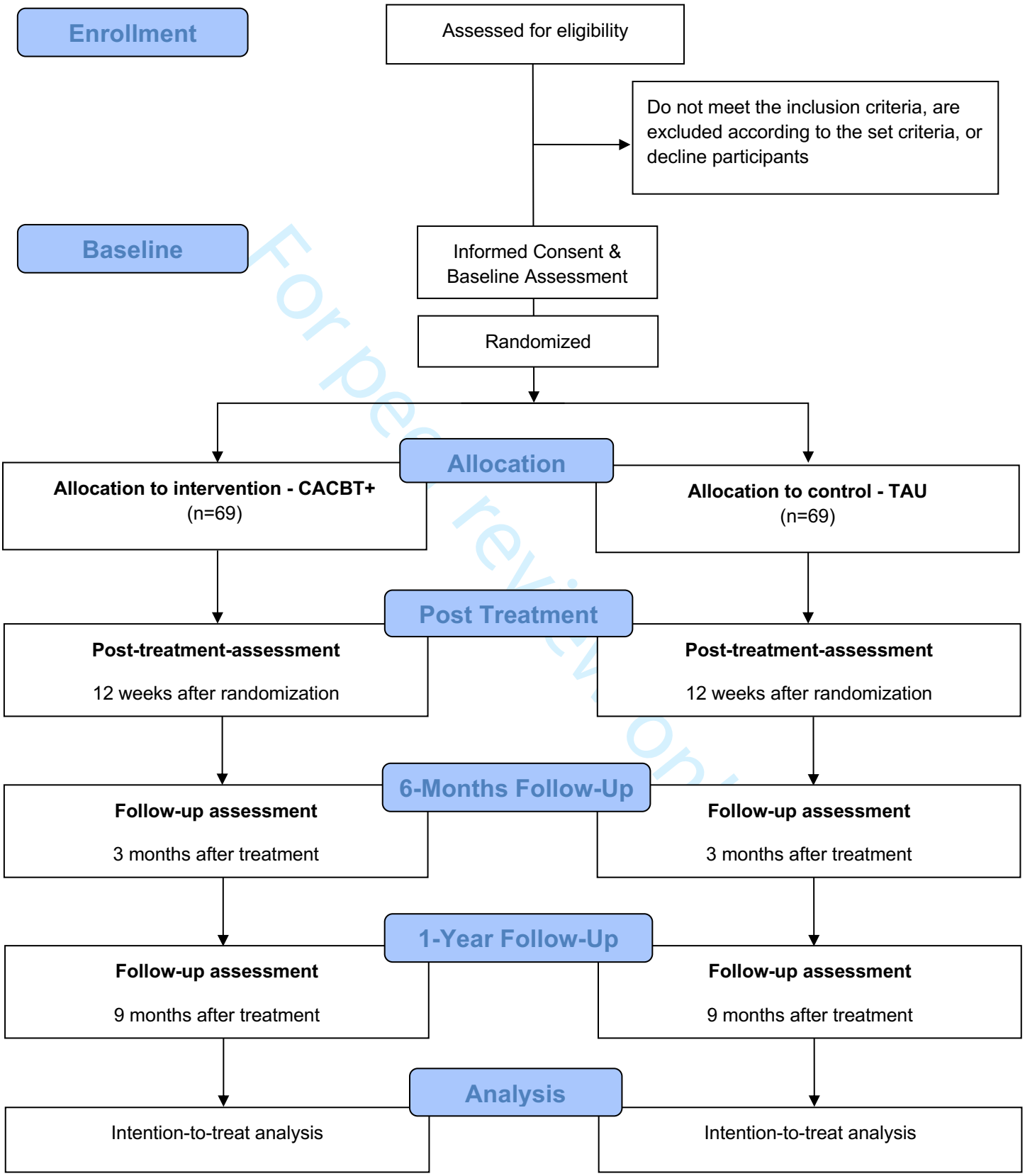
Figure 1 Study flow chart of ReTreat randomised controlled trial. CACBT+, Culturally Adapted Cognitive Behavioural Therapy, TAU, Treatment as Usual.



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title: page 1	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration: page 3	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version: page 3	3	Date and version identifier
Funding: page 1	4	Sources and types of financial, material, and other support
Roles and responsibilities page 1	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale: page 5-7	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives: page 7	7	Specific objectives or hypotheses

Trial design: page 8	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting: page 8	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria: page 8-9	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions: page 11-12	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes: page 12-14	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline: page 9-10	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size: Page 16	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment: page 9	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:
page 10
page 16

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking): Page 16	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods: Page 13-14	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management: page 17-18	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods: page 18-19	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring: page 19	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms: page 16-17	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing: page 17-18	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval: page 19	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments: page 17-18	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent: page 10	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality: page 17	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests: page 19	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data: Page 17	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy: page 19	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.